Cancer Causes and Control **14**: 847–857, 2003.
© 2003 *Kluwer Academic Publishers. Printed in the Netherlands.*

Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort

D. Michal Freedman[1,*], Alice Sigurdson[1], Michele Morin Doody[1], R. Sowmya Rao[2] & Martha S. Linet[1]
[1]*Division of Cancer Epidemiology and Genetics, Radiation Epidemiology Branch, National Cancer Institute, Bethesda, MD, USA;* [2]*Division of Cancer Epidemiology and Genetics, Biostatistics Branch, National Cancer Institute, Bethesda, MD, USA*

Received 9 January 2003; accepted in revised form 26 July 2003

Key words: alcohol, body mass index, height, melanoma, menarche, oral contraceptive use, parity, radiologic technologists, smoking, weight.

Abstract

Objective: To investigate whether smoking, alcohol intake, female hormonal or anthropometric factors affect melanoma risk.
Methods: Using Cox proportional hazards regression analyses, we analyzed 68,588 white subjects (79% female) from the US Radiologic Technologists (USRT) Study who were cancer-free (other than non-melanoma skin cancer) as of the first of two self-administered questionnaires. Follow-up covered 698, 028 person-years, with 207 cases of melanoma.
Results: We found that melanoma risk was not associated with height, weight or BMI, nor with age at menarche, menopausal status, use of hormone replacement therapy, parity, age at first birth or oral contraceptive use. Melanoma risk was elevated with increasing alcohol use (RR: 2.1; 95% CI: 0.9–4.8, for >14 drinks/week compared to never drinking; (p(trend) = 0.08)). Smoking for long durations compared to never smoking was inversely related to melanoma risk (RR: 0.6; 0.3–1.3; ≥30 years; p(trend) = 0.03), though risk was not associated with number of packs smoked per day.
Conclusions: None of the anthropometric or female reproductive/hormonal factors evaluated were related to melanoma risk. It is unclear whether the positive association with alcohol intake and inverse association with smoking for long duration are causal. The alcohol and smoking findings warrant detailed assessment in studies with substantial statistical power where potential biases can be more fully evaluated.

Abbreviations: ARRT – American Registry of Radiologic Technologists; RR – Relative Risk; US – United States; USRT – United States Radiologic Technologists

Introduction

Most epidemiologic studies of cutaneous malignant melanoma have focused on sunlight exposure and risks associated with host susceptibility characteristics, such as skin pigmentation, and eye and hair color [1–3]. A number of studies have also explored the possible contribution of smoking, alcohol use, anthropometric characteristics, and female hormonal factors to melanoma risk [1–23], but available epidemiologic evidence has been inconsistent, with few analyses based on large, prospective cohort studies. To help understand the possible etiologic role of these factors, we evaluated melanoma and smoking, alcohol intake and other characteristics in a large, nationwide

* Address correspondence to: D. Michal Freedman, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Radiation Epidemiology Branch, Executive Plaza South, Room 7036 6120 Executive Plaza Boulevard Bethesda, MD 20892, USA. Ph.: +301-496-6600; Fax: +301-402-0207; E-mail: mf101e@nih.gov

occupational cohort with information about most postulated risk factors collected prior to melanoma diagnosis.

Materials and methods

The US Radiologic Technologist (USRT) Study comprises a cohort of 146,022 radiologic technologists, who were residing in the United States and certified by the American Registry of Radiologic Technologists (ARRT) for at least 2 years between 1926 and 1982 [24, 25]. We mailed a baseline questionnaire to all cohort members who were located and found to be alive (n = 132,454) during 1983–1989. The questionnaire collected information on height, weight, smoking behavior, alcohol use, and female hormonal factors, as well as work history and other factors. A second questionnaire, administered during 1994–1998, ascertained incident cancers, updated information on the risk factors previously evaluated, and asked about skin pigmentation, hair and eye color, as well as family medical history. Sixty-eight percent (90,305) responded to the first questionnaire; among living respondents to the initial questionnaire, 83% (70,859) answered the second questionnaire.

Description of study population

We restricted this investigation to white respondents who responded to the baseline questionnaire, were cancer-free (except for non-melanoma skin cancer) as of the first questionnaire, and responded to the second questionnaire or died during the intervening period through August 1998 (n = 68,588). Eligible cases included both incident melanoma cases (i.e., subjects reporting a diagnosis of primary cutaneous melanoma occurring between completion of the two questionnaires) and deaths (*i.e.*, subjects who died before completing the second questionnaire through August 1998, with melanoma listed as an underlying or contributory cause of death, as determined through linkage with the National Death Index).

Pathology reports and other confirmatory medical records (hereafter the combination of pathology reports and other medical records is designated as medical records) were requested to validate the self-reported melanomas. Among the 243 subjects reporting melanoma, medical records were obtained for 160 (66%). Of these 160, medical records validated the melanoma diagnosis for 140 subjects (88%). We excluded the 20 incorrectly reported 'melanomas' from the case grouping. The 140 validated melanomas, however, included diagnoses of 31 melanomas *in situ* and four ocular melanomas, which were also excluded from the case definition. Principal findings, however, were analyzed both with cases excluding and including the validated *in situ* melanomas.

There were no significant differences by age, geographic region of residence or number of years worked as a radiologic technologist between those potentially eligible cases for whom medical records were and were not obtained. Because a high proportion of self-reported melanomas were confirmed by medical records, and cases whose self-reported diagnoses were or were not confirmed by medical records did not differ significantly by sociodemographic factors, we included potentially eligible incident cases for whom medical record confirmation could not be obtained.

Similarly, decedents were included because of the high (89%) confirmation rate for melanoma designated as a cause of death on US death certificates [26]. Because only first primary cases were eligible, decedents with melanoma and another cancer cause of death listed on the death certificates were included only if the average survival rate of melanoma exceeded that for the other cancer based on average survival rates for that cancer from population-based registries in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program [27] and, thus, likely preceded it (one case was excluded). After exclusions, cases totaled 207, including 193 incident first primary melanomas and 14 deaths.

Data collection

Age (at questionnaire response), gender, height, weight, smoking behavior, alcohol intake, some reproductive factors (age at menarche, use of oral contraceptives, age began using oral contraceptives), education and work history were obtained from responses to the first questionnaire. A proxy measure for mean annual adult residential exposure to sunlight was derived using the estimated annual solar ultraviolet radiation assigned to each state [28] in which the subject reported working weighted by the duration of working in that location. A proxy measure for the potential residential sun exposure during childhood was estimated as the annual solar ultraviolet radiation assigned to each subject's state of birth. Data on hair, eye, and skin color and family history of melanoma were derived from the second questionnaire and, thus, were not available for subjects who had died before completing the second questionnaire. Some time-dependent reproductive factors (menopausal status, use of hormone replacement therapy (HRT), parity, age at first birth) used information from

both questionnaires, if available. When not available, missing information was imputed using nearest neighbor imputation methods [29, 30]. Missing information for non-time dependent variables was coded as a separate unknown category. No information was available from subjects about residential history during childhood (except birthplace), nor about the number of sunburns, skin reactions to sun exposure, or numbers of nevi among subjects.

Statistical methods

We used Cox proportional hazards regression analyses to compute relative risks (RRs) with 95% confidence intervals (CIs), using age at diagnosis or death from melanoma as the response (i.e., age as the time-scale beginning at completion of the first questionnaire) [31], and we stratified the baseline hazard by birth cohort in 5-year intervals. Subjects were followed from the first questionnaire until the date of death, completion of the second questionnaire, or the diagnosis of the first cancer (other than non-melanoma skin), whichever occurred first. Subjects who died due to causes other than melanoma (n = 2261) were included in the analysis as non-cases, despite the absence of some covariate information (*i.e.*, skin pigmentation, hair color) for non-respondents to the second questionnaire. Non-respondents to the second questionnaire, for whom information about incident melanomas was unknown (14,874 subjects who were presumed alive based on tracing using National Death Index, Social Security and other records), were excluded from the analysis.

Multivariate models included gender, smoking duration, alcohol intake and established risk factors for cutaneous melanoma, *i.e.*, skin pigmentation, hair color, personal history of non-melanoma skin cancer, as well as the proxy measures for residential childhood and adult sunlight exposure, education, and decade of

Table 1. Frequency of selected demographic and other characteristics among white melanoma cases compared with the study population of white radiologic technologists in the USRT Study cohort[a]

characteristics	Melanoma cases		Study population	
	n = 207	%	n = 68,588	%
Age at baseline[b]				
<35 years	81	39.1	30,597	44.6
35–44 years	78	37.7	22,877	33.4
45–54 years	32	15.5	9.352	13.6
55–64 years	11	5.3	3763	5.5
65+ years	5	2.4	1999	2.9
Gender				
Female	159	76.8	54,045	78.8
Male	48	23.2	14,543	21.2
Education[c]				
High School (9–12 years)	4	1.9	519	0.8
Radiation Technology Program (2 years)	107	51.7	37,414	54.6
1+ years college/graduate school	88	42.5	26,696	38.9
Other	7	3.4	3520	5.1
Year certified as radiation technologist				
<1950	9	4.4	1951	2.8
1950–1959	29	14.0	8299	12.1
1960–1969	58	28.0	20,052	29.2
1970–1979	101	48.8	34,699	50.6
1980+	10	4.8	3617	5.3
Residence at baseline				
Northeast	40	19.3	17,191	25.1
Southeast	51	24.6	21,866	31.9
Central	63	30.4	17,255	25.2
West	53	25.6	12,266	17.9

[a] Restricted to white respondents to first survey (baseline) questionnaire who were cancer-free (other than non-melanoma skin cancer) at baseline. Some frequencies do not total 100% due to missing information.

[b] Responded to 1st questionnaire (1984–1989).

[c] Subjects were placed in the 'highest' educational category applicable, with college ranked after radiological training, which was ranked after high school education.

employment began as a radiation technologist. In tests for trends, we modeled exposure variables as continuous; *p*-values are two-sided.

Results

The majority of this study population of white and cancer-free members of the USRT cohort were female (79%) and about 45% were younger than 35 years old when completing the baseline questionnaire (Table 1). Follow-up covered 698,028 person-years. Melanoma risk was not associated with gender and varied only modestly with age (Table 2). Constitutional factors (skin, eye, and hair color), personal history of non-melanoma skin cancer, family history of melanoma, and adult 'residential' sunlight exposure were all significantly associated with melanoma (Table 2).

Table 2. Adjusted RR and 95% CIs for melanoma associated with demographic and constitutional factors, personal and family history of skin cancer, and potential 'residential' sunlight exposure index in the white study population of the USRT cohort[a]

Characteristics[b]	No. of cases	RR[c]	95% CI	*p*(trend)
Age (at baseline questionnaire)[d]				
<35	81	1.0	–	
35–44	78	1.4	1.0–1.8	
45–54	32	1.4	0.9–2.1	
55–64	11	1.3	0.7–2.4	
65+	5	1.3	0.5–3.1	0.07
Gender				
Female	159	1.0	–	
Male	48	1.1	0.8–1.5	
Skin tone[e]				
Medium/Dark	53	1.0	–	
Fair	140	2.7	2.0–3.7	
Eye color[e]				
Brown/black	41	1.0	–	
Gray/hazel	40	1.3	0.8–2.0	
Blue/green	112	1.9	1.4–2.8	
Hair color[e]				
Dk. Brown	71	1.0	–	
Lt. Brown	63	1.2	0.8–1.6	
Blonde	37	1.4	0.9–2.1	
Red	22	2.8	1.7–4.4	
Past skin cancer (basal/squamous)				
No	193	1.0	–	
Yes	14	4.5	2.5–7.9	
Family history of melanoma in 1st degree relatives[e]				
No	185	1.0	–	
Yes	8	5.0	2.5–10.2	
Estimated mean annual adult residential sunlight exposure[f] (tertiles)				
1 (lowest)	68	1.0	–	
2	37	0.8	0.5–1.2	
3 (highest)	94	1.6	1.2–2.2	<0.001[g]
Estimated mean childhood residential sunlight exposure[h] (tertiles)				
1 (lowest)	66	1.0	–	
2	60	0.9	0.6–1.2	
3 (highest)	73	1.1	0.8–1.5	0.04[g]

[a] Restricted to white subjects who responded to the baseline questionnaire and were cancer-free (other than non-melanoma skin cancer) at that time.
[b] Missing information was coded in a separate category (not shown).
[c] RR estimated using Cox proportional hazards regression with age as the time-scale, stratified at baseline by birth cohort in 5-year intervals.
[d] This variable alone was analyzed using follow-up years as the time-scale, with no strata at baseline, in Cox proportional hazards regression.
[e] Subjects who died of melanoma, and thus did not respond to the second questionnaire, have missing information for these variables.
[f] Time-weighted average of estimated annual solar ultraviolet radiation (in Robertson–Berger units $\times 10^{-4}$) assigned to each state [28] in which a job was performed and weighted by the duration of the job (tertile cut points: 114, 134).
[g] *p*(trend) based on the underlying continuous variable.
[h] Estimated annual solar ultraviolet (in Robertson–Berger units $\times 10^{-4}$) assigned to the state of birth [28] (tertile cut points: 111, 121).

Table 3. Adjusted RR and 95% CIs of melanoma associated with height, weight, BMI, and female hormonal factors in the white study population of the USRT cohort[a]

Characteristics[b]	Women				Men			
	No. of cases[b], n = 159	RR[c]	95% CI	*p*(trend)[d]	No. of cases,[b] n = 48	RR[c]	95% CI	*p*(trend)[d]
Anthropometric								
Height (quartiles)[e]								
1 (low)	42	1.0			13	1.0		
2	51	1.2	0.8–1.8		10	0.6	0.3–1.5	
3	21	1.0	0.6–1.8		14	0.8	0.4–1.8	
4 (high)	43	1.3	0.8–2.1	0.13	9	0.8	0.3–1.9	0.79
Weight (quartiles)[f]								
1 (low)	36	1.0			7	1.0		
2	37	1.2	0.8–2.0		16	2.6	1.0–6.6	
3	48	1.2	0.7–1.9		12	1.8	0.7–5.0	
4 (high)	35	1.2	0.7–2.0	0.70	13	2.2	0.8–6.1	0.14
BMI (quartiles)[g]								
1 (low)	44	1.0			6	1.0		
2	34	0.8	0.5–1.3		17	2.7	1.1–7.0	
3	37	0.9	0.6–1.4		14	2.1	0.8–5.6	
4 (high)	40	0.9	0.6–1.4	0.95	9	1.4	0.5–4.1	0.85
Hormonal (females)								
Oral contraceptive (OC) use								
Never	34	1.0						
Ever	125	1.2	0.8–1.8					
Past	104	1.2	0.7–1.8					
Current	20	1.4	0.7–2.6					
<5 years	7	1.8	0.8–4.4					
5+ years	12	1.2	0.6–2.4					
Age began OC use								
<20	39	1.0						
20–24	59	1.0	0.6–1.5					
25+	26	1.1	0.6–2.0					
Never	34	0.9	0.5–1.5					
Menopause								
No	104	1.0						
Yes	55	1.0	0.6–1.6					
HRT use								
Never	119	1.0						
Ever	40	1.2	0.8–1.8					
Age at menarche								
≤11	28	1.0						
12	38	1.0	0.6–1.6					
13	48	1.1	0.7–1.7					
14	29	1.6	0.9–2.7					
15+	12	0.9	0.5–1.8	0.50				
Age at first birth								
<25	59	1.0						
25–29	43	0.8	0.5–1.2					
30+	13	0.6	0.3–1.0					
Nulliparous	42	0.9	0.6–1.4					
Parity								
Nulliparous	42	1.0						
Parous	117	0.9	0.6–1.3					
1 child	20	0.7	0.4–1.1					
2 children	56	1.0	0.7–1.5					
3 children	20	0.8	0.5–1.4					
4+ children	14	1.2	0.7–2.4					

[a] Restricted to white respondents to baseline questionnaire who were cancer-free (other than non-melanoma skin cancer) at baseline.
[b] Some frequencies do not total 100% due to missing information.

Table 3. (Continued)

[c] RR estimated using Cox proportional hazards regression analysis with age as the time-scale, stratifying at baseline on birth cohort in 5-year intervals. Adjusted for gender, alcohol intake, years smoked, skin pigmentation, hair color, personal history of non-melanoma skin cancer, decade began work as a technologist, education, and proxy measures for residential childhood and adult sunlight exposure. Height was also adjusted for weight, and weight, for height. Missing information for the characteristics was analyzed with separate dummy variables.

[d] p(trend) based on the underlying continuous variable.

[e] Quartile cut points (meters) in women: 1.6; 1.65; 1.68. In men: 1.73; 1.78; 1.83.

[f] Quartile cut points (kg) in women: 54.4; 59.4; 68.0; In men: 72.6; 79.4; 88.5.

[g] Quartile cut points (kg/m^2) in women: 20.4; 22.1; 24.7; In men: 23.3; 25.1; 27.4.

Melanoma risk was not associated with height, weight or BMI in men or women (Table 3). There was also no association with female hormonal factors, including age at menarche, age at first use of oral contraceptives, age at first birth, number of births, menopausal status or use of HRT (Table 3). Melanoma risk was non-significantly elevated with current oral contraceptive use (at the time of the first questionnaire) compared to never use (RR: 1.4; 0.7–2.6); however, risk did not increase with longer duration of use among current users.

Compared to subjects who never drank alcohol, those who drank more than 14 drinks per week had a nearly significant twofold higher risk (p(trend) = 0.08) (Table 4). The twofold risks associated with drinking more than 14 drinks per week characterized both men and women, though the trend was only significant in women.

A slight non-significant inverse association was observed among current smokers (those who reported smoking at the time of the first questionnaire) compared to non-smokers among the combined group of men and women (Table 4). Similar patterns were evident in men and women assessed separately. Although the risk of melanoma was unrelated to number of packs smoked per day, it was inversely associated with long duration. Risk was 40% lower among those smoking for 30 or more years compared to non-smokers (p(trend) = 0.03). Long duration (25+ years) and high pack years (30+) among current smokers were also both inversely associated with melanoma risk, but only significantly in women and the combined population of men and women. When we examined the risk of residential sunlight exposure by smoking status, we found an elevated risk of melanoma (RR: 2.1; 1.2–3.7; n = 49) associated with indicators of high adult residential sunlight exposure (3rd tertile) in non-smokers, but no association was found between indicators of high adult residential sunlight exposure and melanoma among subjects who smoked cigarettes for 10 or more years (1.1; 0.5–2.2; n = 28) (Table 5). The interaction, however, between smoking and residential sunlight surrogate was not significant. When smoking and alcohol intake were analyzed with cases that included validated cases of *in situ* melanoma, the results were similar (data not shown).

Discussion

The lack of association we found between melanoma and particular anthropometric factors is consistent with many other studies [7, 12, 15, 32,], though not all [13, 18, 21, 33, 34]. Unfortunately, we were only able to assess the effects of anthropometric factors as of the baseline questionnaire (especially important for weight and BMI), and thus could not explore these factors as age-dependent variables. We also found no association with female hormonal factors, which have shown no consistent relationship to melanoma risk in epidemiologic studies [1].

While we found some evidence of a positive association with alcohol consumption, the association was primarily limited to those in the highest consumption category (>14 drinks per week), with a trend that was only significant in women. Our finding of a possible association between melanoma and alcohol intake is in line with a few studies [20, 21, 35, 36], but not others [8, 13, 16, 37, 38]. One of the few prospective studies on this topic [21] observed a borderline significant elevated association with wine consumption that was restricted to women. Our data, however, do not distinguish types of alcoholic beverages and thus cannot identify possible differential associations with these drinks. Few studies have suggested potential biologic mechanisms for a possible relationship between alcohol and melanoma risk, though a pituitary-mediated mechanism has been proposed [35].

The inverse association with smoking duration that we identified in this population between melanoma and cigarette smoking was unexpected. A review of other epidemiologic studies indicate a pattern of inverse associations with smoking in many studies (reviewed in Table 6). There are a number of possible non-causal explanations for the inverse association between mela-

Table 4. Adjusted RR and 95% CIs of melanoma associated with alcohol intake and smoking in the white study population of the USRT cohort[a]

Characteristics	Women				Men				Combined population			
	No. of cases[b]	RR[c]	95% CI	*p*(trend)[d]	No. of cases[b]	RR[c]	95% CI	*p*(trend)[d]	No. of cases[b]	RR[c]	95% CI	*p*(trend)[d]
Alcohol (drinks/week)												
Never	23	1.0			8	1.0			31	1.0		
Ever	136	1.2	0.8–1.9		40	1.5	0.7–3.3		176	1.3	0.9–1.9	
<1–6	114	1.2	0.7–1.9		32	1.5	0.7–3.4		146	1.2	0.8–1.8	
7–14	19	1.7	0.9–3.1		4	0.9	0.2–3.0		23	1.4	0.8–2.5	
>14	3	2.1	0.6–7.0	0.05	4	2.4	0.7–8.2	0.61	7	2.1	0.9–4.8	0.08
Overall smoking status												
Never-smoker	80	1.0			22	1.0			102	1.0		
Ever-smoker	79	1.0	0.7–1.3		26	0.6	0.3–1.1		105	0.9	0.7–1.2	
Former smoker	46	1.1	0.7–1.5		14	0.6	0.3–1.2		60	0.9	0.7–1.3	
Current smoker	32	0.8	0.5–1.3		11	0.6	0.3–1.3		43	0.8	0.5–1.1	
Age first smoked												
Never-smoker	80	1.0			22	1.0			102	1.0		
<16	12	1.0	0.5–1.9		4	0.3	0.1–1.0		16	0.7	0.4–1.3	
16–17	23	1.1	0.7–1.7		4	0.3	0.1–0.9		27	0.8	0.5–1.3	
18–19	20	0.7	0.4–1.2		11	1.1	0.5–2.3		31	0.8	0.5–1.2	
>19	23	1.1	0.7–1.8	0.38	6	0.8	0.3–1.9	0.21	29	1.0	0.7–1.6	0.20
Packs/day												
Never-smoker	80	1.0			22	1.0			102	1.0		
<0.5	28	1.0	0.7–1.6		6	0.7	0.3–1.9		34	1.0	0.7–1.5	
0.5–1	31	0.9	0.6–1.4		8	0.5	0.2–1.2		39	0.8	0.6–1.2	
>1–2	17	0.9	0.5–1.5		9	0.6	0.2–1.3		26	0.8	0.5–1.3	
>2	2	1.4	0.3–5.8	(0.64)	3	1.0	0.3–3.7	(0.20)	5	1.3	0.5–3.4	(0.33)
Duration (years)												
Never-smoker	80	1.0			22	1.0			102	1.0		
<10	24	1.0	0.6–1.6		3	0.4	0.1–1.4		27	0.9	0.6–1.3	
10–19	33	1.1	0.7–1.6		13	1.0	0.5–1.9		46	1.1	0.7–1.5	
20–29	11	0.6	0.3–1.2		4	0.3	0.1–0.9		15	0.5	0.3–0.9	
30+	6	0.6	0.2–1.5	(0.14)	5	0.6	0.2–1.9	(0.07)	11	0.6	0.3–1.3	(0.03)
Pack-years												
Never-smoker	80	1.0			22	1.0			102	1.0		
<10	43	1.0	0.7–1.5		9	0.7	0.3–1.6		52	1.0	0.7–1.3	
10–29	21	0.8	0.5–1.2		9	0.6	0.2–1.3		30	0.7	0.5–1.1	
30+	9	0.8	0.4–1.7	(0.31)	7	0.5	0.2–1.3	(0.25)	16	0.7	0.4–1.3	(0.16)
Duration of current smokers												
Never-smoker	80	1.0			22	1.0			102	1.0		
Current, <15	17	1.5	0.9–2.6		0				17	1.2	0.7–2.1	
15–24	9	0.6	0.3–1.2		6	0.7	0.3–1.9		15	0.7	0.4–1.2	
25+	6	0.5	0.2–1.1	(0.04)	5	0.7	0.2–2.0	(0.17)	11	0.6	0.3–1.1	(0.02)
Pack-years of current smokers												
Never-smoker	80	1.0			22	1.0			102	1.0		
Current, <15	22	1.2	0.7–1.9		2	0.4	0.1–1.9		24	1.1	0.7–1.7	
15–29	5	0.4	0.2–1.0		5	0.9	0.3–2.4		10	0.6	0.3–1.1	
30+	4	0.5	0.2–1.3	(0.03)	4	0.5	0.2–1.6	(0.20)	8	0.5	0.3–1.1	(0.03)

[a] Restricted to white respondents to baseline questionnaire who were cancer-free (other than non-melanoma skin cancer) at baseline.
[b] Some frequencies do not total 100% due to missing information.
[c] RR estimated using Cox proportional hazards regression analysis with age as the time-scale, stratifying at baseline on birth cohort in 5-year intervals. Adjusted for gender, alcohol intake, years smoked (for alcohol), skin pigmentation, hair color, personal history of non-melanoma skin cancer, decade began work as a technologist, education and proxy measures for residential childhood and adult sunlight exposure. Missing information for the characteristics was analyzed with separate dummy variables.
[d] *p*(trend) based on the underlying continuous variable, except for alcohol intake, which was based on a multi-level single variable.

noma and cigarette smoking, including screening bias, inadequate adjustment for sunlight exposure and SES, and ascertainment bias. Screening bias is suggested if smokers obtain fewer preventive screening exams, as suggested by data from the 1998 National Health Interview Survey (NHIS) [42], and the higher risk of

Table 5. Adjusted RR and 95% CIs for melanoma associated with indicators of residential sunlight exposure among non-smokers, short-term smokers (<10 years) and long-term smokers (≥10 years) in the white study population of the USRT cohort[a]

Estimated mean annual adult residential sunlight exposure[b] (tertiles)	Non-Smokers				Smokers (<10 years)				Smokers (≥10 years)			
	No. of cases n = 98	RR	95% CI	*p*(trend)[c]	No. of cases n = 25	RR	95% CI	*p*(trend)[c]	No. of cases n = 71	RR	95% CI	*p*(trend)
1 (lowest)	33	1.0			9	1.0			26	1.0		
2	16	0.9	0.5–1.8		2	0.3	0.1–1.7		17	0.9	0.4–1.9	
3 (highest)	49	2.1	1.2–3.7	<0.01	14	2.0	0.7–6.0	0.04	28	1.1	0.5–2.2	0.54

[a] Restricted to white respondents to baseline questionnaire who were cancer-free (other than non-melanoma skin cancer) at baseline.
[b] RR estimated using Cox proportional hazards regression analysis with age as the time-scale, stratifying at baseline on birth cohort in 5-year intervals. Adjusted for gender, alcohol intake, skin pigmentation, hair color, personal history of non-melanoma skin cancer, decade began work as a technologist, education, and proxy measures for residential childhood sunlight exposure. Time-weighted average of estimated annual solar ultraviolet radiation (in Robertson–Berger units $\times 10^{-4}$) assigned to each state [28] in which a job was performed and weighted by the duration of the job (tertile cut points: 113, 133).
[c] *p*(trend) based on the underlying continuous variable.

late-stage diagnosis [43–45], though the reports of a higher risk of squamous cell carcinoma among smokers [41, 46, 47] provide some counter evidence. Possible bias regarding our inability to adjust for sun exposure is also mixed. The literature suggests that regular smokers may be less likely to use sun protective measures than non-smokers [42, 48, 49], though smokers appear to be less physically active than non-smokers [50, 51] and thus presumably spend more time indoors. It seems unlikely that ascertainment bias could explain the reduced risk of melanoma among smokers, because response to the second questionnaire among smokers (76.4%) was only slightly less than among non-smokers (80.8%).

The apparent absence of an elevated risk of melanoma among long-term smokers with indicators of high residential sunlight in contrast to the increased risk observed in non-smokers could reflect various biases (see above) or chance. We plan to evaluate this finding further in a comprehensive case–cohort study within the USRT cohort focusing on risk factors for melanoma and non-melanoma skin cancer. If the case–cohort investigation or other studies confirm a reduced risk of melanoma among smokers exposed to high levels of sunlight when the sun exposure is more accurately assessed, then it is possible that there may be an inhibitory effect of cigarette smoking on inflammatory skin responses to ultraviolet radiation. Laboratory findings have shown an up-regulation of cycloxygenase (COX)-2 following acute exposure to ultraviolet-B irradiation in cultured keratinocytes [52]. In addition, cycloxygenase is expressed in primary malignant melanomas and melanoma cell lines and appeared to be related to melanoma invasion [53]. Further, a recent case–control study [54], found an inverse association between melanoma risk and regular daily intake of non-steroidal anti-inflammatory drugs (NSAIDS), but not with acetaminophen, which has weak anti-inflammatory properties. Two studies also suggest that cigarette smoking [55] and nicotine [56] reduced the cutaneous inflammatory response to UVB irradiation among human volunteers.

There are several limitations to this study, including the absence of detailed information on sunlight exposure, sunburn history, and the number and kind of nevi, as well as the inability to validate all self-reported melanomas and causes of death. However, when *in situ* cases were included, which increased the case validation rate, the results were similar. Compared to previous, primarily case–control studies, strengths of the investigation include the prospective collection of information on melanoma risk factors. Other advantages include the relatively large number of melanoma cases and the availability of information on some major potential confounders, including constitutional and personal and family skin cancer history.

In this study, generally only established risk factors were significantly and positively associated with melanoma. It is not clear whether the positive association with alcohol intake and inverse association with long duration of smoking are causal. The findings regarding alcohol consumption and smoking warrant more detailed assessment in studies with substantial statistical power where potential biases can be more fully evaluated. If replicated, they warrant experimental studies to explore potential biological mechanisms. Our results have no public health implications for smoking behavior.

Table 6. Summary of odds ratios (OR) and RR for melanoma associated with cigarette smoking overall and by duration daily and cumulative amount in published studies

Study [reference no.] (cases/controls or cases/cohort)	Type of study	Overall OR or RR (95% CI)	Duration	Daily amount	Cumulative amount
Current study[a] 207/ 68,588	Cohort	Ever smoker[a] 0.9 (0.7–1.2) Former smoker[a] 0.9 (0.7–1.3) Current smoker[a] 0.8 (0.5–1.1)	Years[a] <10: 0.9 (0.6–1.3) 10–19: 1.1 (0.7–1.5) 20–29: 0.5 (0.3–0.9) ≥30: 0.6 (0.3–1.3)	Packs/day[a] <0.5: 1.0 (0.7–1.5) 0.5–1.0: 0.8 (0.6–1.2) >1–2: 0.8 (0.5–1.3) >2: 1.3 (0.5–3.4)	Pack-years <10: 1.0 (0.7–1.3) 10–29: 0.7 (0.5–1.1) ≥30: 0.7 (0.4–1.3)
Australia and Scotland [39][b] 275/496 36/72 respectively	Case/control	Former smoker[b] 0.8 (0.6–1.1) Current smoker[b] 0.6 (0.4–0.9)			
Denmark [16][c] 474/ 926	Case/control	Former smoker[c] 1.0 (0.7–1.3) Current smoker[c] 0.8 (0.6–1.1)		Daily no. cigarettes[c] 1–9: 1.1 (0.7–1.5) 10–19: 0.6 (0.4–0.9) 20+: 0.8 (0.6–1.2)	
Montreal [40][d] >103/ 533 pop. controls; 1602 cancer controls	Case/control	Ever-smoker[d] 0.5 (0.3–0.9)			Cigarette-years[d] 1–500: 0.7 (0.4–1.4) 501–1000: 0.5 (0.2–0.9) 1001–1500: 0.4 (0.2–1.0) 1501+: 0.4 (0.1–0.9)
Netherlands [41][e] 125/386	Case/control	Ever-smoker[e] 0.8 (0.5–1.2)			
Norway [21][f] 108/50,757	Cohort	Former smoker[f] 0.9 (0.5–1.4)		Daily no. cigarettes[f] 0–10: 0.6 (0.4–1.1) ≥11: 0.7 (0.4–1.4)	
Queensland, Australia [8][g] 183/236	Case/control	Ever-smoker[g] 0.8			Lifetime No. Packs[g] 1: 0.7 (0.2–2.1) 500−: 0.8 (0.3–2.4) 10,000+: 1.3 (0.3–5.0)
Sweden [22][h] 400/640	Case/control	Ever-smoker[h] 0.9 (0.7–1.2) Former smoker[h] 1.0 (0.3–3.5) Current smoker[h] 0.7 (0.5–1.1)		Daily no. cigarettes[h] 1–19: 0.7 (0.5–1.1) ≥20: 0.6 (0.3–1.1)	
United States [35][i] Male (M): >22 Female (F): >23; <7518	Case/control				Cigarette-years[i] M 1–400: 1.05 401–800: 0.37 >800: 0.52 F 1–400: 1.08 401–800: 0.44 >800: 0.89
United States (Washington County, Maryland)[j] [57] 23/46	Nested case /control	Former smoker[j] 0.9 Current smoker[j] 0.5			
United States (Western Washington State)[k] [18] 386/727	Case/control	Former smoker 0.8 (0.6–1.1)[k] Current smoker 0.6 (0.4–0.8)[k]			

[a] Referent = Never smoker. Adjusted for gender, alcohol intake, skin pigmentation, hair color, personal history of non-melanoma skin cancer, decade began work as a technologist, education and proxy measures for residential childhood and adult sunlight exposure.
[b] Referent = Never smoker. Limited to acral melanoma (on soles and palms). Adjusted for age, gender, social class.
[c] Referent = Never smoker.

Table 6. (Continued)

[d] Referent = Non-smokers. Males only. Total number of melanoma cases not specified; cigarette-years = (average number of cigarettes/day) × (duration of smoking (years)); Covariates include, among others, age, ethnic group, socioeconomic status (as measured by self-reported income), and a blue-collar/white collar 'dirtiness' score.
[e] Referent = Non-smokers. Hospital-based study. Adjusted for age, gender, total amount of sun exposure.
[f] Referent = Never smoker. Adjusted for gender, age at inclusion, county of residence, and the time-scale variable of attained age.
[g] Referent = Rarely/never smoker. Lifetime number of packs adjusted for pigment cell phenotype and lifetime sun exposure.
[h] Referent = Never smoker. Adjusted for history of sunburns and host factors (i.e., hair color, number raised nevi).
[i] Referent = Non-exposed. Neither total number of cases nor controls specified. Adjusted for age and race.
[j] Referent = Never smoker.
[k] Referent = Never smoker. Adjusted for age and sex.

Acknowledgements

We are grateful to the radiologic technologists who participated in the USRT Study; Jerry Reid of the ARRT for continued support of this project; Diane Kampa of the University of Minnesota for data collection and coordination; Kathy Chimes of Westat for data management; Roy Van Dusen and Laura Bowen of Information Management Services, Inc. for computing assistance; Drs Barry I. Graubard, Margaret A. Tucker, and Thomas R. Fears of the National Cancer Institute and Dr DuPont Guerry IV of the University of Pennsylvania for advice. We also wish to acknowledge our appreciation to Drs John Boice, Jr and Jack Mandel who played a critical role in the initiation, design, and follow-up of this cohort study for many years.

References

1. Armstrong BK, English DR (1996) Cutaneous malignant melanoma. In: Schottenfeld D, Fraumeni, JF, Jr. eds. *Cancer Epidemiology and Prevention*. 2nd edn New York: Oxford University Press, pp. 1282–1312.
2. Liu T, Soong S-J (1996) Epidemiology of malignant melanoma. *Surg Clin North Am* **76**: 1205–1222.
3. Weinstock MA (1998) Issues in the epidemiology of melanoma. *Hematol Oncol Clin North Am*. **12**: 681–698.
4. Bain C, Hennekens CH, Speizer FE, Rosner B, Willett W, Belanger C (1982) Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* **68**: 537–539.
5. Beral V, Evans S, Shaw H, Milton G (1984) Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* **50**: 681–685.
6. Feskanich D, Hunter DJ, Willett WC, *et al*. (1990) Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* **81**: 918–923.
7. Gallagher RP, Elwood JM, Hill GB, Coldman AJ, Threlfall WJ, Spinelli JJ (1985) Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada melanoma study. *Br J Cancer* **52**: 901–907.
8. Green A, Bain C, McLennan R, Siskind V (1986) Risk factors for cutaneous melanoma in Queensland. *Recent Res Cancer Res* 1**02**: 76–97.
9. Holly EA, Cress RD, Ahn DK (1994) Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogen. *Cancer Epidemiol Biomarkers Prev* **3**: 661–668.
10. Holly EA, Cress RD, Ahn DK (1995) Cutaneous melanoma in women III. Reproductive factors and oral contraceptive use. *Am J Epidemiol* **141**: 943–950.
11. Holly EA, Weiss NS, Liff JM (1983) Cutaneous melanoma in relation to exogenous hormones and reproductive factors. *J Natl Cancer Inst* **70**: 827–831.
12. Holman CDJ, Armstrong BK, Heenan PJ (1984) Cutaneous malignant melanoma in women: exogenous sex hormones and reproductive factors. *Br J Cancer* **50**: 673–680.
13. Kirkpatrick CS, White E, Lee JAH (1994) Case–control study of malignant melanoma in Washington State II. Diet, alcohol, and obesity. *Am J Epidemiol* **139**: 869–80.
14. Lambe M, Thörn M, Sparén P, Bergström R, Adami HO (1996) Malignant melanoma: reduced risk associated with early childbearing and multiparity. *Melanoma Res* **6**: 147–153.
15. Osterlind A, Tucker MA, Stone BJ, Jensen OM (1988) The Danish case–control study of cutaneous malignant melanoma III. Hormonal and reproductive factors in women. *Int J Cancer* **42**: 821–824.
16. Osterlind A, Tucker MA, Stone BJ, Jensen OM (1988) The Danish case–control study of cutaneous malignant melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. *Int J Cancer* **42**: 825–828.
17. Palmer JR, Rosenberg L, Strom BL, *et al*. (1992) Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* **3**: 547–554.
18. Shors AR, Solomon C, McTiernan A, White E (2001) Melanoma risk in relation to height, weight, and exercise. *Cancer Causes Control* **12**: 599–606.
19. Smith MA, Fine JA, Barnhill RL, Berwick M (1998) Hormonal and reproductive influences and risk of melanoma in women. *Int J Epidemiol* **27**: 751–757.
20. Stryker WS, Stampfer MJ, Stein EA, *et al*. (1990) Diet, plasma levels of beta-carotene and alpha-tocopherol, and risk of malignant melanoma. *Am J Epidemiol* **131**: 597–611.
21. Veirod MB, Thelle DS, Laake P (1997) Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. *Int J Cancer* **71**: 600–604.
22. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N (1996) Risk of malignant melanoma in relation to drug intake, alcohol, smoking and hormonal factors. *Br J Cancer* **73**: 1126–1131.
23. Zanetti R, Franceschi S, Rosso S, Bidoli E, Colonna S (1990) Cutaneous malignant melanoma in females: the role of hormonal and reproductive factors. *Int J Epidemiol* **19**: 522–526.

24. Boice JD, Mandel JS, Doody MM, *et al*. (1992) A health survey of radiologic technologists. *Cancer* **69**: 586–598.
25. Doody MM, Mandel JS, Lubin JH, Boice JD, Jr. (1998) Mortality among United States radiologic technologists, 1926–1990. *Cancer Causes Control* **9**: 67–75.
26. Percy CL, Miller BA, Gloeckler-Ries LA (1990) Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Ann New York Acad Sci* **609**: 87–99.
27. Greenlee RT, Hill-Harmon MB, Murray T, Thun M (2001) Cancer Statistics, 2001 CA. *Cancer J Clin* **51**: 15–36.
28. Scotto J, Fears TR, Fraumeni, JF, Jr. (1996) Solar radiation. In: Schottenfeld D, Fraumeni, JF, Jr. eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York: Oxford University Press, pp. 355–372.
29. Little RJA, Rubin DB (1987) *Statistical Analysis with Missing Data*. New York: John Wiley & Sons, Inc. pp. 65–67.
30. Groves RM, Dillman DA, Eltimpe JL, Little RJA (2002) *Survey Nonresponse*. New York: John Wiley & Sons, Inc. pp. 330–333, 419.
31. Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* **145**: 72–80.
32. Le MG, Cabanes PA, Desvignes V, Chanteau MF, Mlika N, Avril MF (1992) Oral contraceptive use and risk of cutaneous malignant melanoma in a case–control study of French women. *Cancer Causes Control* **3**: 199–205.
33. Thune I, Olsen A, Albrektsen G, Tretli S (1993) Cutaneous malignant melanoma: association with height, weight and body-surface area, a prospective study in Norway. *Int J Cancer* **55**: 555–561.
34. Cutler C, Foulkes WD, Brunet JS, Flanders TY, Shibata H, Narod SA (1996) Cutaneous malignant melanoma in women is uncommonly associated with a family history of melanoma in first-degree relatives: a case–control study. *Melanoma Res* **6**: 435–440.
35. Williams RR, Horm JW (1977) Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* **58**: 525–547.
36. Bain C, Green A, Siskind V, Alexander J, Harvey P (1993) Diet and melanoma: an exploratory case–control study. *Ann Epidemiol* **3**: 235–238.
37. Adami HO, McLaughlin JK, Using AW, *et al*. (1992) Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* **3**: 419–425.
38. Holman CDJ, Armstrong BK, Heenan PJ, *et al*. (1986) The Causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. *Recent Res Cancer Res* **102**: 18–37.
39. Green A, McCredie M, MacKie R, *et al*. (1999) A case–control study of melanomas of the soles and palms (Australia and Scotland). *Cancer Causes Control* **10**: 21–25.
40. Siemiatycki J, Krewski D, Franco E, Kaiserman M (1995) Associations between cigarette smoking and each of 21 types of cancer: a multi-site case–control study. *Int J Cancer* **24**: 504–514.
41. De Hertog SAE, Wensveen CAH, Bastiaens MT, *et al*. (2001) Relation between smoking and skin cancer. *J Clin Onc* **19**: 231–238.
42. Santmyire BR, Feldman SR, Fleischer AB (2001) Lifestyle high-risk behaviors and demographics may predict the level of participation in sun-protection behaviors and skin cancer primary prevention in the United States. *Cancer* **92**: 1315–1324.
43. Van Durme DJ, Ferrante JM, Pal N, Wathington D, Roetzheim RG, Gonzalez EC (2000) Demographic predictors of melanoma stage at diagnosis. *Arch Fam Med* **9**: 606–611.
44. Rigel DS, Friedman RJ, Levine J, Kopf AW, Levenstein M (1981) Cigarette smoking and malignant melanoma: prognostic implications. *J Dermatol Surg Oncol* **7**: 889–891.
45. Shaw HM, Milton GW (1981) Smoking and the development of metastasis from malignant melanoma. *Int J Cancer* **28**: 153–156.
46. Aubry F, MacGibbon B (1985) Risk factors of squamous cell carcinoma of the skin: a case–control study in the Montreal region. *Cancer* **55**: 907–911.
47. Grodstein F, Speizer FE, Hunter DJ (1995) A prospective study of incident squamous cell carcinoma of the skin in the Nurses' Health Study. *J Natl Cancer Inst* **87**: 1061–1066.
48. Coogan PF, Geller A, Adams M, Benjes LS, Koh HK (2001) Sun protection practices in preadolescents and adolescents: a school-based survey of almost 25,000 Connecticut schoolchildren. *J Am Acad Dermatol* **44**: 512–519.
49. Hall HI, Jones SE, Saraiya M (2001) Prevalence and correlates of sun screen use among US high school students. *J Sch Health* **71**: 453–457.
50. Chalmers K, Sequire M, Brown J (2002) Tobacco use and baccalaureate nursing students: a study of their attitudes, beliefs and personal behaviours. *J Adv Nurs* **40**: 17–24.
51. Kimm SYS, Glynn NW, Kriska AM, *et al*. (2002) Decline in physical activity in black girls and white girls during adolescence. *N Eng J Med* **347**: 709–715.
52. Buckman SY, Gresham A, Hale P, *et al*. (1998) COX-2 expression is induced by UVB exposure in human skin: Implications for the development of skin cancer. *Carcinogenesis* **5**: 723–729.
53. Denkert C, Kobel M, Berger S, *et al*. (2001) Expression of cyclooxygenase 2 in human malignant melanoma. *Cancer Res* **61**: 303–308.
54. Harris RE, Beebe-Donk J, Namboodiri KK (2001) Inverse association of non-steroidal anti-inflammatory drugs and malignant melanoma among women. *Oncol Repts* **8**: 655–657.
55. Mills CM, Hill SA, Marks R (1993) Altered inflammatory response in smokers. *BMJ* 3**07**: 911.
56. Mills CM, Hill SA, Marks R (1997) Transdermal nicotine suppresses cutaneous inflammation. *Arch Dermatol* **133**: 823–825.
57. Cornwell ML, Comstock GW, Holick MF, Bush TL. Prediagnostic serum levels of 1,25-dihydroxyvitamin D and malignant melanoma. (1992) *Photodermatol Photoimmunol Photomed* **9**: 109–112.